*Comparative Effectiveness Research Review Disposition of Comments Report*

**Research Review Title:** *Local Hepatic Therapies for Metastases to the Liver From Unresectable Colorectal Cancer*

Draft review available for public comment from June 26, 2012 to July 27, 2012.

**Research Review Citation:** Belinson S, Chopra R, Yang Y, Shankaran V, Aronson N. Local Hepatic Therapies for Metastases to the Liver From Unresectable Colorectal Cancer. Comparative Effectiveness Review No. 93. (Prepared by Blue Cross and Blue Cross Blue Shield Association Technology Evaluation Center under Contract No. 290-2007-10058-I.) AHRQ Publication No. 13-EHC014-EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

## Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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| Commentator & Affiliation | Section | Comment | Response |
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| Peer Reviewer #1 | Clarity and Usability | Given the limited studies of any value and the limited applicability of the data, the review provides appropriate conclusions for policy and practice decision making. | Thank you |
| Peer Reviewer #2 | Clarity and Usability | The report was very well organized and well written. However, I do have some major critiques regarding the collection and review of the data as mentioned above. The final conclusion that a conclusion cannot be made is not surprising but I think is in important point that must be acknowledged given the number of articles reviewed. This publication may result in a unified effort with IR and hepatic surgeons to create a consortium algorithm and patient registry to help determine how best to identify patients and which procedure would best serve the patient and avoid treating those patients that would not benefit from therapy. Furthermore more randomized studies are needed to compare systemic chemo vs. systemic chemo plus liver directed therapies. | Thank you for the careful reading of this report. We believe we have addressed your concerns adequately. A comparison of systemic chemotherapy versus systemic chemotherapy plus liver directed therapies is outside the scope of this report. The scope of this review was determined with input from the Key Informants and Technical Expert Panel. |
| Peer Reviewer #3 | Clarity and Usability | The report is well structured and organized and the main points are clearly presented. As mentioned the conclusions can be used to direct future research but because of the variability in the literature, at this time it is impossible for this literature review to inform policy and practice decisions. This of course is not the fault of the actual report but represents a common problem in the device industry including devices with therapeutic intent. | Thank you |
| Peer Reviewer #4 | Clarity and Usability | The report is well structured. However, it is very detailed and needs an executive summary. | We apologize if you did not see the executive summary, but it is present in the report from pages ES1-ES23 |
| Peer Reviewer #6 | Clarity and Usability | The Discussion section is very well written, insightful and thought-provoking. The Research Gap section is worth review by all oncology clinicians caring for patients with metastatic colorectal cancer. | Thank you |
| Peer Reviewer #7 | Clarity and Usability | Overall this is a great report that should incent future research to close the gaps identified. | Thank you |

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| Peer Reviewer #8 | Clarity and Usability | The report is well structured and organized. However, there is redundancy/repetitiveness in the executive summary and the main body of the manuscript.<br><br>At this point, I do not think health care policy and/or practice decisions should be made on the information presented. Many of these studies show survival benefit and therapeutic effectiveness. However, there is little in terms of comparative effectiveness. Given that many of the patients have no other options after exhausting therapies given to them, I do not believe that these interventions should be withheld based on the lack of currently available data. | Thank you, the overlap in the executive summary and main report reflects the importance of those key points to both documents.<br>We agree that evidence is insufficient to permit conclusions on effectiveness of these liver-directed therapies compared to one another, but it is outside the scope of the report for the authors to comment on if these treatments should be withheld from patients. |
| Peer Reviewer #1 | General Comment | The report is well written and structured in a way that allows the reader to understand the intent of the review, the manner in which the data were collected, and the method of analysis. The key questions are clearly stated and the review is well focused to addressing the key questions. The key points and recommendations are succinctly and clearly stated. | Thank you |
| Peer Reviewer #2 | General Comment | The selection process of the studies selected was very thorough. Overall, the report is very meaningful to all medical oncologists that treat metastatic colorectal cancer despite not having any conclusive evidence based on existing presented or published data. I was a coauthor on the ASCO paper (Reference #30) and we faced similar challenges. It signifies the continued need to identify the best patient population for local hepatic therapies as well as the continued unmet need for clinical research in this patient population including quality of life. It would be beneficial if we could determine that liver directed therapy has no role in those patients whose disease is refractory to standard chemotherapy as I suspect will be the case but the data is not strong enough to support this concept. | Thank you |
| Peer Reviewer #2 | General Comment | My primary concern for the evaluation is that the expert panel was largely composed of medical oncologists and interventional radiologists. One important component that was missing from this expert panel was the hepatic surgeons. Many of them previously used to do HAI and many complete RFA's on patients. | While the addition of a hepatic surgeon may have made our panel more comprehensive we do not feel that the addition of this member would have substantially changed the key questions outcomes or comparators of the review. |
| Peer Reviewer #2 | General Comment | A future cost benefit analysis would also be helpful. | Currently analyses involving cost effectiveness are not undertaken by AHRQ. |

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| Peer Reviewer #3 | General Comment | The authors have identified a topic of very significant importance since patients with liver metastases secondary to colon cancer represent a large group of individuals. It is well recognized that patients are considered for a host of different liver directed therapies and yet the guidance for use of such is extremely limited. This report is critical since it clearly outlines the issues, provides an extensive review of the literature, and demonstrates that the quality of the literature is so poor that it is impossible to create a guidance document. The report outlines the gaps in knowledge and should form the basis as to structuring future prospective assessments of liver directed therapies. Of note, these conclusions are comparable to those from the American Society of Clinical Oncology report on the use of just one of the liver directed therapies, radio-frequency ablation for colorectal liver metastases, that was published in the Journal of Clinical Oncology in 2010 and thus reinforces the fact that commonly utilized procedures often have an inadequate body of evidence to guide the use of such interventions. | Thank you |
| Peer Reviewer #4 | General Comment | The report is clinically meaningful but not useful. Due to lack of evidence this report fails to identify the best if any method for local management of metastatic colon cancer.<br>The target population and key questions are properly defines. | Thank you |
| Peer Reviewer #5 | General Comment | One thing I found ambiguous was the purpose of the analysis. Was the comparative effectiveness being evaluated among different liver-directed therapies, or of liver directed therapy in general compared to standard of care systemic therapy? | The purpose of this review was to compare the comparative effectiveness and harms of liver-directed therapies in two patient populations: unresectable, chemo-refractory patients with minimal extrahepatic disease and unresectable, non-extrahepatic disease where liver-directed therapy is an adjunct to chemotherapy. We did not attempt to compare liver-directed therapy to standard of care systemic therapy. There were no studies that compared liver-directed therapies to one another in our literature search. |
| Peer Reviewer #5 | General Comment | Gaps, bullet point 2: while it is of some interest eventually to obtain comparative effectiveness data within the various classes of liver-directed therapies (e.g., radiofrequency vs. microwave ablation, chemoembolization vs. radioembolization), these are secondary goals at this time. The pressing primary goal is to demonstrate survival benefit in the setting of current standard of care, an extremely daunting task. If and when this has been accomplished, then attention can turn to comparison among techniques, which are continuously evolving. | The scope of this review was focused on comparisons of two liver directed therapies. The comparison to systemic chemotherapy and resection were outside the scope of the review. We are precluded from going outside the scope of the review when identifying evidence gaps of interest. |

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| Peer Reviewer #6 | General Comment | The target population is well defined in the introduction. | Thank you |
| Peer Reviewer #6 | General Comment | The key questions are stated with some inconsistencies throughout the report as it relates to whether either of the two clinical scenarios could or should include patients with "no" or "little" extrahepatic disease. This is very relevant clinical detail as the report indicates in terms of defining comparators. | Within the PICOTS table for this CER the report erroneously stated “no or minimal extrahepatic disease” for KQ3 and 4. This has been changed to “no extrahepatic disease” to reflect the correct inclusion criteria for these key questions. We believe we have been otherwise distinguished where in the report extra-hepatic disease was present.<br><br>Patients for key questions 1 and 2 were eligible for inclusion if the authors stated that the extent of extra-hepatic disease was limited and that the tumor burden was liver-dominant. For key questions 3 and 4 patients were excluded if extrahepatic disease was present. However, because of the paucity of evidence in the literature, and the heterogeneity of patient populations, we included studies where extrahepatic disease was present if this occurred in less than 10% of the patient population. We have footnoted these instances where appropriate. |
| Peer Reviewer #6 | General Comment | The target audience is well characterized on page 43. I would include radiation oncologists and surgeons mentioned in those professionals providing clinical care. | The sentence now reads *“Treatment is generally provided by medical oncologists, radiation oncologists, interventional radiologists, and surgeons.”* |
| Peer Reviewer #7 | General Comment | The report concisely gathers the relevant and available information, presenting it in an unbiased fashion. It is clinically relevant and hopefully will encourage further research to address the gaps identified. | Thank you |

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| Peer Reviewer #8 | General Comment | The report is a comprehensive and detailed review of the currently available data on locoregional therapies for unresectable colorectal hepatic metasases.<br><br>While there are numerous studies assessing the utilization and benefit of locoregional therapies for metastatic colorectal cancer to the liver, the main issue presented is that there are very few "good" studies making valid conclusions impossible. That said, it does appear that there is survival benefit and quality of life improvements but there is little data comparing specific interventions head-to-head.<br><br>Funding and prospective randomized controlled trials are strongly needed to truly evaluate the effectiveness of these therapies.<br><br>One issue that was not addressed in this mansucript was when patients become refractory to systemic chemotherapy and then offered locoregional therapies to the liver. The authors use the term "refractory" to describe those patients that progress despite chemotherapy. However, it is well known that for systemic therapy, patients do much better when they are chemonaive or exposed to little chemotherapy. Unfortunately, many if not most patients who are referred for locoregional therapies have already undergone many chemotherapy regimens and ultimately progressed. Therefore, the underlying liver is already damaged and the patients are selected to do worse as a result, no matter what locoregional therapy is offered. Further, many of these therapies in the palliative category are for patients who have ran out of other options. These issues should be addressed somewhere in the review. | Thank you. We do address the issue that many of these patients had previous systemic treatment or, in some instances, previous liver-directed therapies in a transparent manner in our evidence tables. Additionally, in the discussion we identify heterogeneity in patient treatment history and patient characteristics as severe limitations to meaningful comparison of patient groups.<br><br>With regard to an apparent survival benefit and quality of life improvement from local-hepatic therapies, we believe that this comment is unclear. It is uncertain what the reviewer means by survival benefit and quality of life improvements. As the reviewer states there were no comparative studies, and in the absence of such studies conclusions about benefits to survival and quality of life between the interventions discussed in this CER cannot be reached. |
| Peer Reviewer #1 | Introduction | The Introduction (pp.1-7) provides an appropriate summary. Table 2 well documents the current approach to local modalities of therapy. | Thank you |
| Peer Reviewer #2 | Introduction | Please note the Condition section is incorrect. CRC is the 3rd most commonly diagnosed cancer. | We have edited this sentence to reflect that CRC is third most commonly diagnosed cancer and included an updated reference as per your recommendation. |
| Peer Reviewer #2 | Introduction | Overall very well written introduction and agree with the acknowledgment of the importance of patient registries. | Thank you |

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| Peer Reviewer #3 | Introduction | There are several corrections that should be made in the introduction as follows:<br><br>On page 10/164, beginning with line 34, the authors state that "approximately 1/3 of new cases are diagnosed in the localized state (ie no metastases)…The remaining 2/3 of patients are initially diagnosed with distant (ie metastatic) disease". This is very misleading and should be rewritten. In fact the majority of patients are diagnosed with what is considered as localized disease, including those with stage III colon cancer who have regional lymph node involvement which is contained within the resection specimen. It is estimated that only about 25% of patients truly present with metastatic disease. The authors are urged to refer to and reference the AJCC Staging Manual 7th Edition 2010 to discuss colorectal cancer statistics. In particular it is important to recognize that within stage II and III disease, there are 6 different subtypes of patients for whom there are very significant differences in survivorship. Likewise, beginning with slide 43 (Treatment of Localized Disease), this should also be re-worded since it is misleading. | Thank you for this opportunity to improve the introduction. We have replaced survival data in the section indicated with AJCC 7th edition estimates derived from SEER data. Where data was not available in the AJCC report we have supplemented this with statistics from seer.cancer.gov.<br><br>The new text reads as follows:<br>*Approximately 39 percent of new cases are diagnosed in the localized state, (i.e., no metastases or spread to regional lymph nodes); 36 percent present with regional spread to lymph nodes; 20 percent present with distant, metastatic cancer; and 5 percent present with unstaged disease. The 5-year survival rate estimated by the National Cancer Institute Surveillance Epidemiology and End Results program (SEER) data analysis was found to be 74.1 percent for stage I, 64.5 percent for stage IIA, 51.6 percent for stage IIB, 32.3 percent for stage IIC, 74 percent for IIIA, 45 percent for IIIB, 33.4 percent for IIIC, and 6 percent for stage IV.* |
| Peer Reviewer #3 | Introduction | This section then discusses the stage III patients. As mentioned, stage I, II, and III patients are the majority of those who initially present with colorectal cancer with only a minority presenting with true metastatic disease. Again, it would be important to emphasize that the stage III colon cancer population represents three different subsets who vary in terms of projected outcome even if they have had adjuvant chemotherapy. It is true, however, that clinical trials, including those reporting adjuvant therapy with an oxaliplatin containing regimen, tend not to segregate out survivorship by the substages of patients. | We agree with this comment and have presented data in the introduction according to the new AJCC classification system which reflects the subsets mentioned in this comment. Additionally we have updated the statistics on the number of patients presenting with metastatic disease to reflect the most recent SEER data. |
| Peer Reviewer #3 | Introduction | On page 11/164, line 20, under "Surgery", it would be helpful to mention at some point that at the time of surgical resection of liver metastases, some patients also receive radio-frequency ablation, particularly for lesions that are not well suited for resection. | The following sentence has been added<br>*" Some patients with lesions not well suited for resection may also receive radio-frequency ablation at the time of surgery."* |
| Peer Reviewer #4 | Introduction | Well developed. | Thank you |

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| Peer Reviewer #6 | Introduction | pg 33: definition of two "major indications" for local hepatic therapy. I would argue neither care scenario is an indication for local hepatic therapy. As the content of the introduction implies, these are areas of clinical interest for use of these techniques. | The sentence has been edited to read *"Local hepatic therapy may be used for the following case scenarios."* |
| Peer Reviewer #6 | Introduction | pg 34: substantial # of RFA procedures performed by surgeons and typically by laparoscopic or open surgical approach. | Surgeon has been added to the list for RFA. |
| Peer Reviewer #7 | Introduction | The audience is clearly identified, with the key questions explicitly stated. | Thank you |
| Peer Reviewer #8 | Introduction | The authors do a reasonable job at introducing the topic and issues associated with colorectal cancer metastatic to the liver and define adequately the key questions to be addressed. | Thank you |
| Peer Reviewer #1 | Methods | The methods of study, selection, data extraction, quality assessment, and analysis are all appropriate and well described. | Thank you |
| Peer Reviewer #2 | Methods | Please see general comments section. It is still unclear to me why some hepatic surgeons did not participate in the expert panel. | While the addition of a hepatic surgeon may have made our panel more comprehensive we do not feel that the addition of this member would have substantially changed the key questions, outcomes or comparators of the review. |
| Peer Reviewer #2 | Methods | It is unclear to me as to why liver directed therapy alone was not included as part of this analysis. | The scope of the review was liver-directed therapy versus liver-directed therapy. Systemic chemotherapy alone was not a relevant intervention or comparator for this review. Only the RFA combined with systemic chemotherapy arm was abstracted and included in this report as it is relevant for KQ 3 and KQ 4.<br>The scope of this review was determined with the input from the key informants and the technical expert panel. |
| Peer Reviewer #2 | Methods | For patients with oligometastic surgically unresectable disease, they still provide some underlying knowledge base for QOL. | This report included patient with at most limited extrahepatic spread. Patients with oligometastatic surgically unresectable disease were outside the scope of this review as defined by the technical expert panel and key informants. |

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| Peer Reviewer #2 | Methods | Secondly to capture QOL for KQ's 1 and 2 will be confounded by the fact these are patients that have failed all lines of chemotherapy and already have other constitutional symptoms. | We attempted to assess quality of life data for all of the studies meeting our inclusion criteria, but as you can see from summary table 4 only 3 of 32 studies reported these outcomes. While confounding may be an issue we had insufficient evidence to permit any synthesis. |
| Peer Reviewer #2 | Methods | Review of the included studies indicate several were retrospective series which can further confound the results since it is likely data is missing within those studies at baseline. | The quality of the data included in this review was low poor with no prospective randomized trials. We agree that confounding may occur here and have attempted to reflect this low strength of evidence in our insufficient GRADE conclusions. |
| Peer Reviewer #2 | Methods | Was there a minimal number of patients required to be considered for the analysis? | No |
| Peer Reviewer #2 | Methods | I think PFS is also of great interest not just OS and should be considered as an important analysis needed for future cost benefit analysis. | PFS where presented is in the appendix D. |
| Peer Reviewer #2 | Methods | Also it is unclear to me in the patient population identified that use liver directed therapy as an adjunct to systemic chemotherapy what line of therapy were these studies conducted in? | For key question 3 and 4, patients receiving adjunct chemotherapy, these patients had not received previous chemotherapy so this would be a first line treatment. |
| Peer Reviewer #2 | Methods | Were these patients deferred by liver surgeons for resection first? | The specific protocols for deeming a patient unresectable and presumably vary by institution. However, all patients included in this review were deemed unresectable by their physician. |
| Peer Reviewer #3 | Methods | The methodology appears to be appropriate and represents a comprehensive search of the literature with clear inclusion and exclusion criteria. The search strategies are clear as are the definitions of the criteria for outcome measures. The statistics are extremely limited, as the authors' stress, because of the inconsistency and variability of the studies that are analyzed. | Thank you |
| Peer Reviewer #4 | Methods | The inclusion and exclusion criteria for studies are reasonable and the outcome measures are appropriate. | Thank you |
| Peer Reviewer #5 | Methods | page 16, Key Points bullet 3:<br>The emphasis on reporting size and number of metastases as a measure of st quality is only applicable to ablative therapies, not embolotherapies. For KQ1 and 2 which are for the salvage setting, ablative therapies would rarely be employed.<br>This is repeated top of page 19 as well. | While we agree that ablative therapies would rarely be used in this setting based on the limited data it is unclear which therapies are most effective. Therefore ablative therapies were included and there are two RFA studies. |

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| Peer Reviewer #5 | Methods | page 22, Gaps, bullet point 1:<br>QOL is a minor and not relevant outcome measure in liver-directed therapy. The vast majority of patients are asymptomatic from the liver metastases; hence, palliation of symptoms is a rare indication for liver-directed therapy, even among patients who have progressed following standard 2nd-line systemic therapy and are being treated in a salvage setting. Since the morbidity of liver-directed therapies is minimal and rarely persistent, adverse effects of therapy on QOL is also moot. | We do not agree that QOL is a minor and not relevant outcome for patients. Patient quality of life may be one of the most important outcomes especially when a cure is not the expected therapeutic outcome. Input from Key informants also placed QOL as an important outcome. |
| Peer Reviewer #5 | Methods | Pages 54-ff. The detailed analysis of the papers is handicapped by excessive simplification. Data reported in the papers is listed as absent if not conforming to arbitrary criteria: means vs. medians, for example, or reporting of tumor control rates as absolute percentages vs. actuarially. For example, Albert, Cancer 2011.<br>page 54, Table 6 states median/range of age not reported -- it was as mean and range | We apologize for this oversight, it has been corrected. We attempted to include all relevant data with footnotes or other delineation if the reported data deviated from the listed category. We have double checked the patient and tumor characteristics to ensure no other errors. |
| Peer Reviewer #5 | Methods | page 104 -- A rating of “poor” quality is given to papers missing two variables, but the most common missing variable was acknowledgment of funding. Since most are single institution retrospective series, there is no funding or sponsorship to acknowledge; hence the absence of such is not an omission from the paper -- an inappropriate reason to label study quality “poor” or “fair”, and falsely characterizes the sources used | We appreciate your comment. The overwhelming issue is the lack of comparative data in this literature base. Regardless of the quality of these single arm studies the literature base is insufficient to permit conclusions on the comparative effectiveness of these interventions. We modified our approach. Reporting of sponsorship is no longer considered as a factor in our individual study quality assessment. This will not impact the overall GRADE conclusions. |
| Peer Reviewer #5 | Methods | Gaps, bullet point 3:<br>This is overly simplistic. We are dealing with two entirely different populations: those amenable to ablation, who are viewed similarly to candidates for surgical resection in terms of prognostic and technical factors; and those with more advanced disease who can only have their entire disease burden treated by some form of embolotherapy. The<br>MSKCC clinical risk score applies to candidates for surgical resection, and can be extrapolated to ablative therapies. Size and number of tumors is not relevant for stratifying embolotherapy patients; instead, % tumor burden can be used. Portal vein invasion is a feature of primary liver tumors, very rare in metastatic disease, and would not be used in this patient population. Among prognostic variables mentioned in this document, only performance status is relevant. | The list of variables given here is an example only and not intended to be exhaustive of the differences within these patient population. Within the literature of this report, patient and tumor characteristics were reported inconsistently prompting us to highlight this gap as it impacted our ability to differentiate patient subgroups. The mention of the MSKCC clinical risk score was intended as an example of how a composite measure of risk could be created, in this instance for surgical patients, which could serve as a guide for whom these liver-directed therapies could be applied. We disagree that only performance status is relevant as a prognostic factor as data were too, and analysis too infrequent, within this literature to reach such a conclusion. |

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| Peer Reviewer #6 | Methods | The inclusion/ exclusion criteria seem reasonable overall. Defintion of "liver dominant" disease can be quite variable although as long as it is applied equally within this analysis, unlikely to affect conclusions. | Thank you. We attempted to apply uniform criteria to all of the studies including assessing the extent of extra-hepatic disease. |
| Peer Reviewer #6 | Methods | Quality assessment of studies was well planned and fair. The statistical methods seem sound. | Thank you |
| Peer Reviewer #6 | Methods | I found the mention of intermediate health outcomes in Key Findings and Strength of Outcomes confusing: mention of time to recurrence for KQ 3&4 but all population groups have presumably small # that were truly rendered NED by the interventions, so time to progression or progression-free survvial may have been more appropriate intermediate health outcomes for which to search. | We did extract data on progression free survival and presented it in Appendix D of the comparative effectiveness review. The intermediate outcomes of interest were defined before completing our literature search so we did not know the extent to which this measure would be unreported within the limited literature on this key question. |
| Peer Reviewer #7 | Methods | The outcomes measures are very appropriate as are the statistical methodologies. The strategy for approaching the large # of studies is well thought out and transparent. | Thank you |
| Peer Reviewer #8 | Methods | The methods appear logical reviewing only English articles from 2000-2011. The authors did use MEDLINE and EMBASE for the literature search. Despite more than 800 articles reviewed by the authors, it is suprising and disappointing that more than 97% of studies originally found on this topic were excluded from analysis based on many factors/weaknesses of various papers. | Thank you. It is not uncommon for a search string to yield such a low number of included items. We try to craft a robust enough query that will capture any potential articles of interest. |
| Peer Reviewer #1 | Results | The studies selected for inclusion in this review are appropriately summarized in Table 6. The relevant information is provided in the table. The description of the review and the summary provided clearly shows that all relevant studies have been identified and included. | Thank you |
| Peer Reviewer #2 | Results | Overall, I found the studies included to be reasonable of fair detail. However, I see that many include SIRS spheres (12 of the 23). I would be concerned about selection bias since your expert panel is led by interventional radiologists. I am well aware that interventional radiologists are trying to find a role for SIRS spheres in the day to day treatment of mCRC patients. | The expert panel had no role in article selection or in the analysis. Articles were selected by a prior selection criteria defined by the EPC. |
| Peer Reviewer #2 | Results | For table 6, it would be helpful to see how many patients were evaluated in each study and what line of therapy did these patients receive their treatment? | The number of patients evaluated is in the first column of table 6. Per your suggestion, we have extracted data on previous lines of chemotherapy for all studies present in this table and presented these in Appendix Table D-10. |
| Peer Reviewer #3 | Results | The authors provide appropriate tables which help guide the interpretation of the results. There are no obvious studies that have been overlooked particularly since the overall quality of the literature is so poor. The results clearly justify the authors' conclusions. | Thank you |

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| Peer Reviewer #4 | Results | The results are very detailed and although helpful can be confusing. | Thank you, we have attempted to synthesize these details as clearly as possible. |
| Peer Reviewer #5 | Results | The largest western series on chemoembolization (n=463) does not appear in the analysis:<br><br>Radiology. 2009 Jan;250(1):281-9.<br>Repeated transarterial chemoembolization in the treatment of liver metastases of colorectal cancer: prospective study.<br>Vogl TJ, Gruber T, Balzer JO, Eichler K, Hammerstingl R, Zangos S. | This study was excluded since it was thought that studies with treatment interventions prior to year 2000 would not be applicable to current care due to changes in treatment practices. This study began recruitment in 1999 and was excluded based on our criteria. Additionally as non-comparative study this study would not have impacted the overall GRADE conclusions of the report. |
| Peer Reviewer #5 | Results | Nor do I see two of the seminal papers on radiofrequency ablation, with large numbers and long-term follow-up:<br><br>1. Five-year survival in 309 patients with colorectal liver metastases treated with radiofrequency ablation.<br>Gillams AR, Lees WR.<br>Eur Radiol. 2009 May;19(5):1206-13. Epub 2009 Jan 10. | The paper by Gillams et al., was excluded because of extra-hepatic disease in 37% of the patients and was not described as liver-dominant disease or minimally extra-hepatic disease. Additionally, an unknown number of patients who had extra-hepatic progression were given systemic chemotherapy which would make them ineligible based on our inclusion criteria. |
| Peer Reviewer #5 | Results | 2. Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer:<br>long-term results in 117 patients.<br>Solbiati L, Livraghi T, Goldberg SN, Ierace T, Meloni F, Dellanoce M, Cova L, Halpern EF, Gazelle GS. Radiology. 2001 Oct;221(1):159-66. | The article by Solibati et al was excluded due to a treatment period before year 2000. |
| Peer Reviewer #5 | Results | Table 6 implies absence of ECOG scores -- reported and statistically analyzed, just not in same format as table | We have taken this item under consideration and re-abstracted this field. Several changes were made to table 6 to include a broader range of ECOG scores for these studies and should address the reviewer's concerns. |
| Peer Reviewer #5 | Results | page 60, table 8 states TTP and TTLP not reported, both are reported | Based on a review of the Veltri article resulting from this comment we have excluded this paper as the treatment period began in 1996, which makes the paper ineligible for inclusion in this review. Based on this exclusion the comment is moot. |
| Peer Reviewer #5 | Results | page 66, Table 10, indicates certain specific complication as not reported. The paper used CTC criteria, absence of higher grade indicates severe complications such as biloma and liver failure did not occur; "not reported" is not accurate. | This comment has been noted and the adverse events for liver failure and biloma in the study by Vogl et al. is not reported as 0%. |

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| Peer Reviewer #6 | Results | Results section is very thorough and descriptive. The relevant literature seems to have been thoroughly scrutinized and focused appropriately on more modern studies. | Thank you |
| Peer Reviewer #7 | Results | The bibliography is quite extensive and well presented. It is clear which stduies met the criteria for inclusion and which did not and why. The data is well presented in the figures and tables, making it easy to review and understand the information. | Thank you |
| Peer Reviewer #8 | Results | The Results are well described.<br><br>A few comments came up when reviewing Table #2 (on page 6). For DEB-TACE, suggest removing term "novel" in mechanism of cell death column. While the use of DEBs is more recent, this material is should no longer be considered novel.<br><br>In my opinion, there should be more detail in the Tables with regards to previous treatments (i.e., cycles and types of systemic chemotherapy given before liver directed therapy is initiated. | Thank you<br><br>We have removed the term novel from the table.<br><br>We have added these to appendix D. |
| Peer Reviewer #1 | Discussion/ Conclusion | The findings and the implications of those findings are clearly stated with appropriate summary comments and points. The findings are appropriately stated as to the current quality of the data, relevance to current practice, and definable steps that can be taken to conduct new research. | Thank you |
| Peer Reviewer #2 | Discussion/ Conclusion | Overall, the authors concluded and stated that the results indicate there is significant heterogeneity in the studies that were evaluated re: appropriate patient population (i.e., number and size of lesions), procedure methodology, avg duration of hospitalization, etc. There are clear unmet needs to capture these patients as well as determining which patients should not undergo these procedures. | This appears to be a restatement of our conclusions, thank you. |
| Peer Reviewer #2 | Discussion/ Conclusion | Additionally a cost benefit analysis should be conducted. | Currently analyses involving cost effectiveness are not undertaken by AHRQ. |

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| Peer Reviewer #3 | Discussion/ Conclusion | The implications of the major findings are quite clear. The authors also elucidate the limitations of the studies. They provide a helpful summary of gaps in knowledge which should serve as the basis of conducting future studies. In addition, the authors acknowledge that in the future registry studies be the most direct way to obtain the necessary information to measure the true efficacy of liver directed therapies despite the limitations of such. The authors might mention that there are a prospective trials at least for radioembolization and therefore it would be helpful if the authors did a search of TrialCheck, for example, to ascertain what trials might be available at this time. This would also offer an opportunity to discuss the pro's and con's of these ongoing trials which admittedly will be fairly limited in number. | Thank you for the comment. We did assess in our literature search the completed and ongoing trials for the liver-directed therapies in this report. To address your comment we have included the our identified clinical trials in Appendix D-9.<br>None of these studies are comparative. |
| Peer Reviewer #3 | Discussion/ Conclusion | Of additional note, on pages 22-23/164, "Study Designs to Address These Gaps", the authors provide an appropriate list of challenges which are barriers to conducting randomized controlled clinical trials evaluating liver directed therapies. In this section they might also include that under regulatory guidance, devices (and the liver directed therapies are considered devices even though they are therapeutic in use), do not require the same level of evidence as is required for drug approval by the FDA. Since device companies can routinely obtain reimbursement under current regulations, there is often no incentive for these companies to conduct large scale clinical trials and to pay for the devices under investigation. | The following has been added to the discussion *" Lack of funding sources will continue to be an issue under the current regulatory structure. Under this system devices do not require the same level of evidence as is required for drug approval by the FDA. Since device companies can obtain approval without data from RCTs there is little incentive for them to provide funding. "* |
| Peer Reviewer #4 | Discussion/ Conclusion | The future research provisions are clearly defined based on the available data. | Thank you |
| Peer Reviewer #5 | Discussion/ Conclusion | Overall I agree with the general conclusion. No high-quality RCT's exist for liver-directed therapies for colorectal liver mets. However, the reasons for this and the possible approaches are oversimplified in this document as detailed in my comments. | Thank you, we have addressed your additional comments. |
| Peer Reviewer #5 | Discussion/ Conclusion | Furthermore, it is certainly reasonable to draw broad conclusions from the ample literature available. The large experience with ablation of liver metastases indicates long-term outcomes similar to that achieved by surgical resection. In the majority of studies, actuarial survival following embolotherapies exceeds the expected survival with systemic therapy alone by a substantial margin, both in the salvage setting and when employed earlier in the disease course. Small randomized trials of radioembolization and DEBIRI support this impression (Gray, Aliberti) | The purpose of this review was to compare the effectiveness of the various liver-directed therapies. Comparison to resection or systemic therapy is outside the scope of this review. |

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| Peer Reviewer #5 | Discussion/ Conclusion | page 22-23 , Study Designs to Address Gaps<br>again, this discussion is overly simplistic and neglects critical barriers to clinical research in image-guided liver-directed therapies.<br><br>1. IO trials are very difficult to design. Systemic therapy trials treat all tumors in the body at the same time, definitions of response and progression are standardized, and progression anywhere defines failure of therapy. In contrast, image-guided therapies treat tumors piecemeal. Since not all tumors are treated at the same time, time dependent outcomes such as TTP and PFS are hard to define. RECIST criteria do not work for image-guided therapies, and alternative imaging measures of response such as necrosis and functional imaging have not been validated. Progression does not define failure of therapy, since embolization and ablation can be repeated multiple times. Designing these trials is a nightmare. | We agree that these trials are very challenging to design and implement. As our conclusion states we believe the most important outcomes to be overall survival, QOL and adverse events. |
| Peer Reviewer #5 | Discussion/ Conclusion | 2. They are difficult to accrue. To show survival benefit requires a randomized controlled trial. Trials typically have very strict inclusion and exclusion criteria, which exclude the majority of patients with the disease. Making matters even more challenging, the control arm for most IO trials is either a systemic therapy or supportive care. Given a choice between standard-of-care only versus adding some cutting-edge image-guided therapy, patients want what they perceive is in their best interests, which is to add the image-guided therapy. Since these treatments are available to them off trial, patients do not want to enroll in studies and take the risk of being randomized to the control arm. Hence, only a small percentage of potential patients are both eligible and willing to enroll. | We appreciate the challenges for patient enrollment. We do not however believe that this obviates the need for the data. |

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| Peer Reviewer #5 | Discussion/ Conclusion | 3. Pivotal studies are expensive, lengthy, and do not fit the business plan for devices.<br>The FDA has raised the bar considerably, requiring long-term clinical endpoints such as progression-free or overall survival. These studies take several years and cost tens of millions of dollars. Even if successful, it takes additional years for FDA approval, development of CPT codes and RVU valuations for a novel device.<br>Pharmaceutical companies can invest billions in a new drug, expecting many years of patent protection, and do not require a CPT code. The lifespan of medical devices is shorter than the cycle of clinical trial and approval; by the time a device company completes a study, competitors have built a better mousetrap and jumped into the market with a 510k approval based on the lead companies' device. This regulatory environment is hostile to proper device development and testing, resulting in the plethora of ablation devices and novel embolics entering the market on generic approvals and marketed for off-label use. | The following has been added to the discussion to add this important point<br>*"Lack of funding sources will continue to be an issue under the current regulatory structure. Under this system devices do not require the same level of evidence as is required for drug approval by the FDA. Since device companies can obtain approval without data from RCTs there is little incentive for them to provide funding."* |
| Peer Reviewer #5 | Discussion/ Conclusion | The proposal for an IO registry is misguided. A registry will not advance the critical issues that need to be answered through high quality scientific studies. Neither the FDA nor payers accept registry data for approval. | We agree that the registry does not answer all questions nor will it provide RCT data. The aim is to increase the rigor of the observational data that is currently being collected in the hopes of generating hypothesis to be tested in clinical trials. With the backing of strong observational data some of the identified barriers to research may be mitigated. |
| Peer Reviewer #6 | Discussion/ Conclusion | Major finding bullet point #3 on page 78 should read: The assessment of applicability of the study findings to clinical practice is limited by the poor characterization of the patient populations and lack of randomized trial data to justify generally expensive, potentially toxic and directed therapy for an ultimately systemic disease for the vast majority individuals over the course of their disease. | We have changed the statement to:<br>The assessment of applicability of the study findings to clinical practice is limited by the poor characterization of the patient populations (e.g. number and size of metastases, performance status) and variations in the delivery of the interventions(e.g. surgical approach and dose and drugs delivered) |
| Peer Reviewer #7 | Discussion/ Conclusion | No important studies were excluded. The tables and descriptions clearly convey the key findings of the available literature, including gaps that should be addressed in the future. | Thank you |

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| Peer Reviewer #8 | Discussion/ Conclusions | The implications of the major findings are clearly stated. It is apparent that there is much more work to be done in this area. While there has been benefit in overall survival and quality of life shown in the available literature in this patient population, comparisons among the various types of therapies head-to-head are unavailable. Further, there are considerable limitations to getting appropriate RCTs done in this area as many patients and physicians have concerns regarding randomization and funding for such studies is limited.<br><br>There do not appear to be major omissions in important literature. | Thank you |